

## EPINEPHRIN HYPERSENSITIVENESS AND ITS RELATION TO HYPERTHYROIDISM.\*

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THERE are at the present time two procedures in extensive use in this country for the determination of functional hyperactivity of the thyroid gland. One of these, the measurement of the basal metabolism, rests on sound experimental and clinical observations, for there is abundant evidence that stimulation of the thyroid gland or administration of its active principle induces an increase in heat production. There can be little doubt that stimulation of metabolism is an important feature in hyperthyroidism and that the measurement of the metabolism is a valuable index of the degree of activity of the thyroid gland; but we are still in the dark as to how far other associated features combine with this and go to make up the clinical symptomatology of hyperthyroidism. The outstanding drawback to this method for the determination of thyroid activity is that even with the recently simplified technical procedures it requires specialized training and experience both for its application and for the proper interpretation of the information derived from it.

The second procedure consists of the injection of epinephrin and its diagnostic significance depends on the type of reaction which has been described as occurring in patients with hyperthyroidism, and which is supposed to be characteristic of this condition. The test is usually carried out by the method suggested by Goetsch, and 0.5 c.c. of a 1 to 1000 solution of epinephrin is administered.†

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† The tests were actually carried out in the following manner, as described by Wearn and Sturgis (Arch. Int. Med., 1919, xxiv, 247): "The patients remain at absolute rest in bed for a period of one hour. If there is restlessness or apprehension they should be reassured and every effort made to obtain mental as well as physical quiet. At the end of the rest period control readings of the blood-pressure, pulse- and respiratory-rates are made at five-minute intervals. Also at this time a note is made as to the presence of nervousness, precordial pain, dizziness, palpitation or any other symptoms which may be significant. Likewise the objective condition of the patient is observed, and it is recorded if any of the following signs are present: tremor of the hands, sweating, coldness of the hands, throbbing of the neck, epigastrium or over the precordium and pallor or flushing. At the end of an hour's rest in bed the patient is usually quiet and has few complaints; the blood-pressure and heart-rate are normal or there may be a slight tachycardia (in sharp contrast to the patient with exophthalmic goiter in whom a more marked tachycardia persists even when at rest in bed). Likewise after the rest period there is little to record from an objective or subjective standpoint. If this condition

The "positive" reaction which has been assumed to indicate hyperthyroidism consists of the production of a rise of systolic blood-pressure of at least 10 mm. of mercury or a rise in pulse-rate of at least 10 beats per minute, together with an increase of such signs and symptoms as tremor, sweating, vascular pulsation, nervousness and palpitation. The test is so easy to apply and apparently so simple to interpret that it has been widely adopted as a diagnostic measure, and the "positive" reaction is frequently considered as an indication even for surgical interference. On account of this tendency to regard the test as highly specific in its significance, it has seemed to be of importance to study in more detail the nature of the reaction to epinephrin and to determine the conditions under which the "positive" reaction, which may be assumed to indicate epinephrin hypersensitiveness, appears. Such studies have been carried on at U. S. Army General Hospital No. 9, Lakewood, N. J., and at the Peter Bent Brigham Hospital, Boston. The present communication is a brief summary of the results.

As far as is known the difference between "positive" and "negative" reactions to epinephrin is a quantitative one, and what clinical significance the test possesses depends on the selection of a proper differentiating dose. Even so small an amount as that used (0.5 c.c. of a 1 to 1000 solution) probably produces some effect in everyone. In subjects reacting wholly "negatively" it has been found that the basal metabolism is temporarily raised from 5 to 15 per cent., while in those reacting "positively" the increase is from 15 to 30 per cent.<sup>2</sup> No such effect is observed, even in nervous subjects, from the prick of a needle or from the injection of salt solution. Under given circumstances the effect of the drug seems to remain fairly constant in a given individual.

A fundamental part of the investigation obviously consists of approaching the normal has not been attained then the control readings should continue further, for with nervousness, tremor, sweating, tachycardia or possibly other prominent signs already present it would be difficult to judge the effect of the epinephrin. In a few patients the control readings of blood-pressure and pulse remained at a level slightly above the normal, but the injection of epinephrin was carried out after they became constant. In a number of patients venepuncture was done at the end of the rest period for blood-sugar determinations, but when this or any other disturbing factor is introduced it is necessary that subsequent control readings be made, and these should agree with the preliminary readings before the test can proceed. After satisfactory control readings have been made, 0.5 c.c. of a 1 to 1000 solution of epinephrin, freshly prepared, is injected deep into the deltoid muscle. In all of these tests the solution was made by adding one  $\frac{1}{200}$  grain of Parke, Davis & Co. adrenalin brand of epinephrin tablet to 1 c.c. of water, thereby making a 1 to 1000 solution. After the injection four or five readings are made of the blood-pressure, pulse- and respiratory-rates at two or three-minute intervals, and also at these times any change in the objective or subjective condition of the patient is noted. After the first few observations readings are continued at five-minute intervals until one hour after the injection, when ten-minute readings are made for a period of one-half hour, thus making the observation period one and a half hours from the time of the injection. From our experience at Lakewood it would seem that the time of observation could safely be cut to one hour, as we have failed to observe anything of importance after that length of time."

the "control" observations carried out on normal individuals. These were begun in the army, and it was soon found that the problem was complicated by the fact that our standards of normality were not clearly defined. A number of patients in the hospital for minor surgical ailments turned out to be hypersensitive to epinephrin. Analysis of their past histories and of their characters suggested that while they were normal men, judged by the usual standards, they were not the types from which good soldiers are made. From the point of view of the army the "normal control" must be the soldier who can withstand the strain of hard training. A group of 26 men from an organization which had undergone training for fourteen months and was on its way overseas were therefore studied and none of these were found to give "positive" reactions to epinephrin. These were, of course, selected normals, for they were men of unusual physical endurance and nervous stability. A second group of normal men tested consisted of 28 Harvard medical students, and among these 4, or 14 per cent., gave perfectly definite "positive" reactions. Four other men showed transient rises of pulse-rate of over ten beats per minute, or of a systolic blood-pressure of more than 10 mm., or both. But as these were usually noticed only on one observation and not accompanied by the characteristic symptoms they were not regarded as giving "positive" reactions. In many other "negative" cases slight increase in blood-pressure and pulse-rate were noted. In addition to this there is a third group which may also be properly considered among the normals. These were patients at General Hospital No. 9 on whom the diagnosis of "effort syndrome" was made—men who, for the most part, would pass in civil life as within the bounds of normality but who developed symptoms, usually of a psychoneurotic nature, under the nervous and physical strain of army life. The exact nature of this condition is still uncertain, but there is very general agreement that hyperthyroidism plays no part in it. The clinical picture is not similar to that of hyperthyroidism; the subjects improve under therapeutic measures that make patients with hyperthyroidism worse, and the basal metabolism is normal. If so common a condition as "effort syndrome" represented even a mild or incipient type of hyperthyroidism it is almost inconceivable that definite cases should have been so rare in the army. Among 143 cases of "effort syndrome," 69, or 48 per cent., reacted "positively" to the epinephrin test. These results are not unlike those obtained by Boas,<sup>3</sup> who reports that 28 per cent. of 21 cases of "effort syndrome" gave "positive" reactions. In association with this type of subject one may also consider the observations made on a small number of definite psychoneurotics—individuals who cannot be classed as wholly normal because the symptoms arising in the course of a normal life induced them to seek medical advice, but persons, on the other hand, in whom no evidence of organic disease,

either of the thyroid gland or of any other organ, could be found. Among 7 such subjects all were found to give "positive" reactions to epinephrin.

Summarizing the observations made on the various groups of subjects without evidence of organic disease, one finds that hyper-

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	HANDS	MISCELLANEOUS
9.00	—	—	—	—	COLD	RESTING QUIETLY
9.05	—	—	—	—	"	"
9.10	—	—	—	—	"	"
9.15	EPINEPHRIN 0.5 CC. 1:1000 SOLUTION INTRAMUSCULARLY				COLD	RESTING QUIETLY
9.15 V. S.L.	—	—	—	—	"	"
9.21	—	—	—	—	"	"
9.24	—	—	—	—	"	"
9.27	—	—	—	—	"	"
9.30	—	—	—	—	"	"
9.35	—	—	—	—	"	"
9.40	—	—	—	—	"	"
9.45	—	—	—	—	"	"
9.50	—	—	—	—	"	"
9.55	—	—	—	—	"	"
10.00	—	—	—	—	"	"
10.05 V. S.L.	—	—	—	—	"	"
10.10	+	—	—	—	"	"
10.15	+	—	—	—	"	"
10.20	+	—	—	—	"	"
10.25	+	—	—	—	"	"
10.30	+	—	—	—	"	"

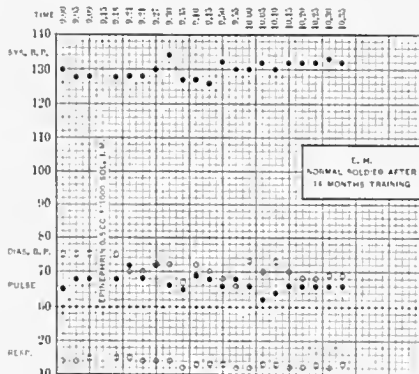


CHART I

sensitiveness to epinephrin is certainly not characteristic of the hardened soldier, that it occurs in about 14 per cent. of average young men, such as medical students, that it is present in nearly 50 per cent. of the type of young men who broke down under military training with the picture of "effort syndrome" and that it is still more common among definite psychoneurotics. It is difficult not

to see some relation between epinephrin hypersensitiveness and what one may call a "nervous constitution." On account of what is generally accepted as being known about the physiologic action of epinephrin, one is tempted to regard the test as indicating a hypersensitiveness of the sympathetic nervous system. It is frequently possible to select, on the basis of clinical study, the subjects who

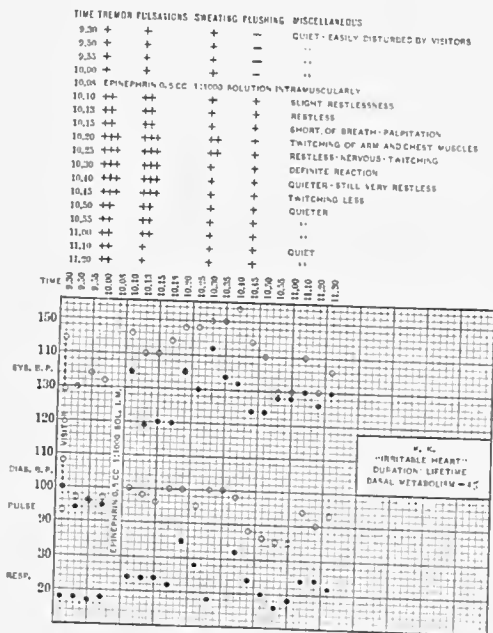


CHART II

will react to epinephrin, but this is by no means always the case. Even after considerable experience with the test one is liable to fall into error. There are many highly "nervous" or "neurotic" people who do not react "positively," and there are occasional persons who have no apparent neurotic tendencies who react violently to the drug.

The epinephrin test has also been used on various other types of

hospital case. Among 17 patients with organic heart disease, 3, or 17 per cent., gave "positive" reactions. This corresponds closely with the 14 per cent. of "positive" reactions found in the group of medical students, and it is possible that the figure represents approximately the average incidence of the reaction among normal persons. Incidental observations have also been made on cases of syphilis, chorea, asthma, acromegaly, epilepsy, diabetes, dementia precox and hyperthyroidism, and one or more "positive" results have been obtained in each condition. In a series of 21 patients who were convalescent from acute infections, 12, or 57 per cent., gave "positive" reactions—a figure in close agreement with results obtained by F. M. Smith,<sup>4</sup> who found that 50 per cent. of 50 cases following influenzal pneumonia reacted "positively." Nicholson and Goetsch<sup>5</sup> report 19 "positive" reactions among 40 cases of questionable or definite tuberculosis, a percentage incidence of 47. One case observed at General Hospital No. 9 seems particularly worth noting. A boy with an organic heart lesion, but otherwise normal, gave a "negative" test. A few days later he had an attack of acute tonsillitis which was followed by a tonsillectomy. A repetition of the test, after convalescence from the operation, gave a "positive" result. This evidence certainly suggests that infections may induce a hypersensitiveness of the sympathetic nervous system, and there are, of course, various clinical symptoms which are in harmony with such a conception. To assume, however, that there is necessarily an associated hyperacidity of the thyroid gland seems quite unwarranted, if only for the reason that many of these post-infectious cases improve with graduated exercises, a type of treatment wholly unsuited to patients with hyperthyroidism. It is true that in certain cases with hyperthyroidism the condition has apparently manifested itself after some acute infections disease, but the reverse is still more striking, for the development of outspoken hyperthyroidism after acute infections is without question more rare than it would be if there were stimulation of the gland in nearly one-half of the cases of acute infections disease.

Case.	Disease.	Positive.	Negative.	Doubtful.
2	Pneumonia . . . . .	2	0	0
3	Diphtheria . . . . .	2	1	0
9	Acute rheumatic fever . . .	4	4	1
1	Acute tonsillitis (tonsillectomy)	1	0	0
6	Scattered . . . . .	3	3	0

Special attention has been paid to the epinephrin test in hyperthyroidism. The diagnosis in the cases reported on was based on the classic signs and symptoms and the history, together with the determination of the basal metabolism. Twenty-one cases have been studied, and in 15, or 71 per cent., "positive" reactions were obtained; 6 unquestionable cases, 4 in early stages and 2 in later stages, with basal metabolism ranging between 21 and 35 per cent.

above normal, gave "negative" epinephrin reactions. No relation was noted between the intensity of the reaction to epinephrin and the apparent severity of the case. One patient, with a basal metabolism 61 per cent. above normal, was considered to be extremely toxic but gave a comparatively slight reaction, while a mild case, with a basal metabolism 26 per cent. above normal, gave a very severe reaction. Nine patients were tested on whom thyroidec-

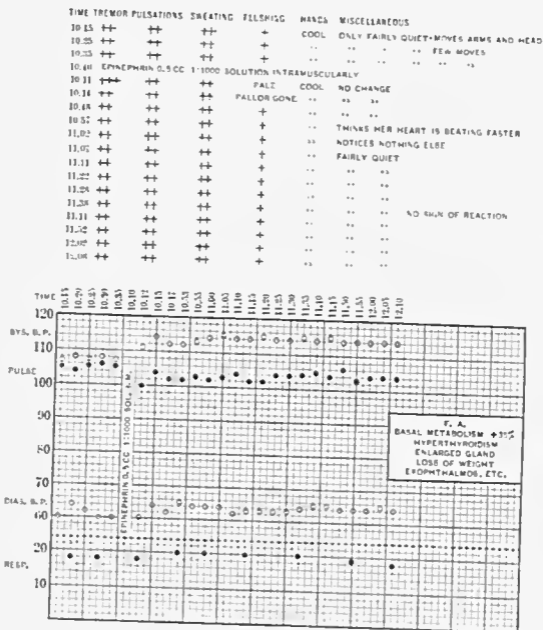


CHART III.

tomies had been done two or three years previously and who had been living normal lives without symptoms for a year or more. Five of them gave "negative" reactions, while 4, in whom the basal metabolism was -18 per cent., -15 per cent., -1 per cent. and +12 per cent., gave "positive" reactions.

The general conclusions which it seems justifiable to draw from our observations are as follows:

1. Different individuals, both sick and well, react with different degrees of intensity to the injection of epinephrin. By means of selected dosage of the drug and carefully chosen criteria for the response, one can differentiate, somewhat artificially, between the slight reactions which are called "negative" and the more violent

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	MISCELLANEOUS
3.15	++	++	+	++	VERY RESTLESS—MOVING CONSTANTLY
3.20	++	++	+	++	" " " "
3.22	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY				" " " "
3.25	++	+	+	ELT FALLOR	RESTLESS AND MOVING
3.30	++	+	++	+	RESTLESSNESS INCREASING
3.32	+++	++	+++	+++	NERVOUS, EXCITED, THROBING
3.35	+++	+++	+++	+++	NERVOUSNESS INCREASING, APPREHENSIVE
3.40	+++	++++	+++	+++	MARKED REACTION
3.45	+++	+++	+++	+++	SOMEWHAT QUIETER
3.50	+++	+++	+++	+++	" "
4.00	+++	+++	+++	+++	" "
4.05	+++	++	++	++	NERVOUSNESS DECREASING
4.15	++	++	++	++	" "
4.25	+++	++	++	++	" "
4.45	+++	+	++	++	" "
4.55	+++	+	++	++	STILL MORE RESTLESS THAN AT START

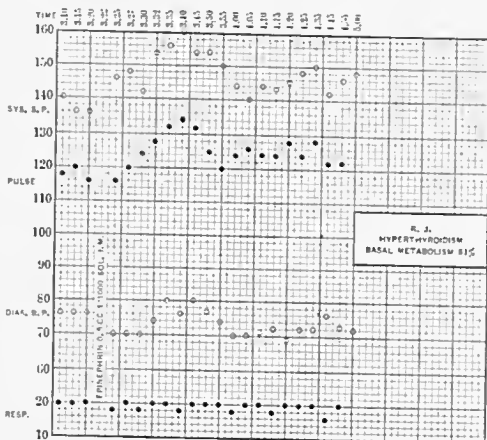


CHART IV

reactions which are called "positive." In certain instances "doubtful" or "questionable" reactions are obtained.

2. The fundamental nature of the reaction is unknown. It is associated with a rise in heat production which runs more or less parallel to the intensity of the reaction. On the basis of what is definitely understood with regard to the physiologic action of

epinephrin it seems probable that the phenomenon is due to a stimulation of the sympathetic nervous system. Theoretically a

TIME	TREMOR	PULSATIONS	SWEATING	FLUSHING	RABDS	MISCELLANEOUS
9.30	+	+	-	+	WARM	QUIET
9.55	+	+	-	+	..	..
10.07	EPINEPHRIN 0.5 CC 1:1000 SOLUTION INTRAMUSCULARLY					
10.05	++	++	-	+	WARM	QUIET
10.07	+++	+++	+SL.	SL. PALLO	COOL	RESTLESS AND NERVOUS
10.10	+++	+++	+	+	..	MORE RESTLESS AND GENERALLY NERVOUS
10.15	+++	+++	+	+	..	REACTION INCREASING
10.20	++++	++++	+	+	..	..
10.25	++++	++++	++	+	..	..
10.30	++++	++++	++	+	..	..
10.35	++++	++++	++	+	..	..
10.40	++++	++++	++	+	..	..
10.45	++++	++++	++	+	..	..
10.50	++++	++++	++	+	..	..
10.55	++++	++++	++	+	..	..
11.00	++++	++++	++	+	..	..
11.05	++++	++++	++	+	..	..
11.15	++++	++++	+	+	..	..
11.25	++++	++++	+	+	..	..
11.35	++++	++++	+	+	..	..

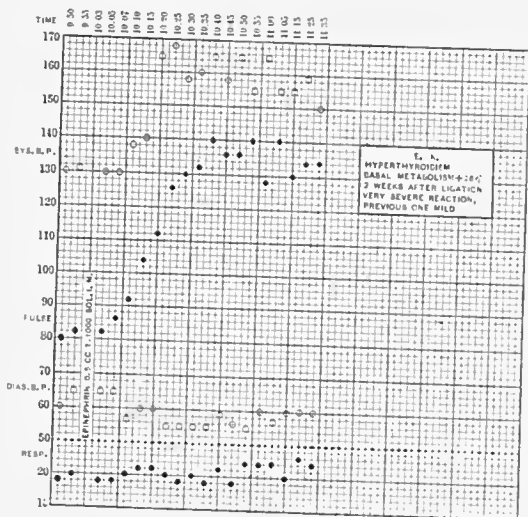


CHART V

"positive" reaction might indicate hyperactivity of the thyroid gland, of the adrenal glands or of the sympathetic nervous system. It might, on the other hand, depend on a lowered threshold of

response of the sympathetic nervous system. With the exception of hyperthyroidism little is known about these conditions in man, but they probably occur and there would seem to be no reason for assuming that a "positive" epinephrin reaction is constantly associated with hyperthyroidism. It is much more likely that different causes account for the reaction in different types of clinical cases.

3. Hypersensitiveness to epinephrin is found in many patients with the clinical picture of hyperthyroidism and with an increased basal metabolism, but it is not constant under these conditions.

4. Hypersensitiveness to epinephrin is also found in persons who have no indications of hyperthyroidism. Thus it was present in many psychoneurotics in about 50 per cent. of patients convalescent from acute infections, in nearly the same proportion of soldiers with "effort syndrome," in 14 per cent. of apparently normal young men and in patients with various unrelated diseases.

5. The "positive" reaction to epinephrin appears to occur most often in highly nervous individuals, but it is not constant in such persons. The clinical significance of the reaction is not clear, but at present it should certainly not be regarded as having any specific significance in the diagnosis of hyperthyroidism.

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### THE USE OF DIET IN THE TREATMENT OF CHRONIC ARTHRITIS.

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IN a series of previous contributions the writer has published the results of laboratory and clinical studies upon chronic arthritis which reached their fullest development in the course of observations upon soldiers in the army.<sup>1</sup> The scale upon which these last observations were conducted was much larger than has heretofore been possible in this country under controlled conditions, and in addition to yielding side lights upon existing views, afforded further data and directed attention along new lines.

<sup>1</sup> Pemberton, Buckman, Foster, Robertson, Tompkins: *Studies on Arthritis in the Army Based on Four Hundred Cases*, *Arch. Int. Med.*, March, 1920, xxv, 231-282; April, 1920, xxv, 335-404.